EXHIBIT 1, Tab 2b

(A) Effect of Activated Charcoal

Study # GB 102:

This study was designed to determine whether oral charcoal could reduce the plasma levels of A77 1726 in man by interruption of the entero-hepatic recycling. This was a pilot study conducted in one healthy male volunteer and the details of the design are outlined on page A30 of the Appendix.

The half-life values for A77 1726 were estimated using a combination of linear regression and method of residuals (Wagner). Values were estimated over the time intervals:
0-120 h (when leflunomide was given alone)
120-122 h (after the first dose of activated charcoal)
122-144 (after the next 2 doses of activated charcoal)
144-360 h (after the effect of charcoal ceased)

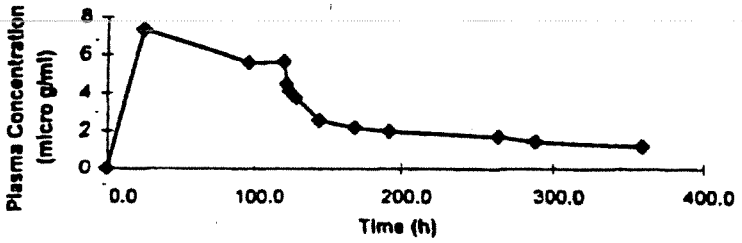


Figure: Plasma concentration of A77 1726 after 100 mg leflunomide and 3x50 g doses of activated charcoal (120, 123 and 126 hours)

After a single dose of 100 mg leflunomide, plasma concentrations of A77 1726 declined with a half life of 240 hours. In a 2 h period following the first 50 mg dose of charcoal the half life decreased to 7 h (5.8 h as calculated by the reviewer). Following the next 2 doses of charcoal (over the period of next 22 hrs) the half-life decreased to 29 h. 18 hrs after the last dose of charcoal (when the effect of charcoal had ended) the half-life returned to a value of 228 h.

(B) Effect of Cholestyramine

Study # GB 104:

In vitro experiments have shown that cholestyramine binds more than twice as much A77 1726 (per gram dry weight) as charcoal. Cholestyramine was also effective in enhancing the elimination of A77 1726. The changes in the half-lives of A77 1726 before and after administration of cholestyramine are shown in the table below. Cholestyramine (8 g each) was administered at 77.5, 83.5, 96, 215.5 and 221.5 hrs after dosing of leflunomide (20 mg dose). The half-lives have been calculated during the time interval of 77.5→96

hours. The third dose of cholestyramine was given at 96 hours (day 5). Details of study are on page A31.

The maximum drop in the half-life is observed after the first and second dose of cholestyramine which were given on day 4. This was followed by a single dose of cholestyramine on day 5. The half-life increases to ~ 104 hours at the 96→216 hr time interval. And once again after the last two doses of cholestyramine at 215.5 and 221.5 hours, the half-life again decreases to ~58 hours.

SPECIAL POPULATION

In Dialysis Patients

Study # B101 NI:

The effects of continuous ambulatory peritoneal dailysis (CAPD) and hemodialysis of the pharmacokinetics of A77 1726 was investigated in this study. Leflunomide (100 mg) was administered to 3 patients on hemodialysis and three on CAPD after the dialysis or after a CAPD bag change. Plasma samples were collected for 28 days after administration of leflunomide and samples from dialysate fluid (CAPD patients) were obtained during the first 3 days. Dialysate of hemodialyzed patients was taken 5 minutes

after start, during (2 hours) and at the end of the first dialysis session performed after drug administration. Dialysate from CAPD patients were taken before leflunomide administration and from all subsequent dwell periods up to 3 days after drug administration. For details see page A32.

- *A77 1726 in plasma*

The individual pharmacokinetic parameters (mean ± sd) of A77 1726, obtained following oral administration of 100 mg leflunomide to hemodialysis patients and CAPD patients is compared with another oral 100 mg leflunomide single dose study in healthy volunteers (Study GB101). In CAPD patients the pharmacokinetic characteristics of A77 1726 were similar to those obtained in healthy volunteers after single dose administration of the drug.

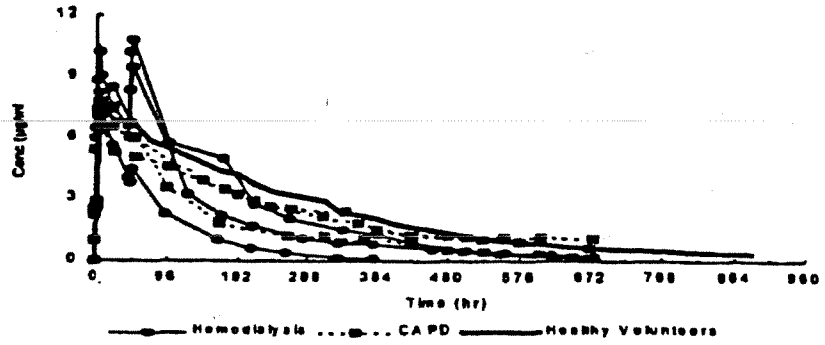


Figure: Individual patient plasma A77 1726 concentrations after administration of 100 mg leflunomide to patients undergoing hemodialysis or CAPD, compared to healthy volunteers from study GB 101.

Parameter	Hemodialysis	CAPD	Healthy Volunteers
C_{max} (µg/ml)	9.2 ± 1.8	7.5 ±0.4	7.6 ± 1.4
t_{max} (days)	1.4 ± 1.1	0.22 ±0.09	0.50 ± 0.4
$AUC_{0-\infty}$ (µg.hr/ml)	1303.9 ± 623.2	1854.9 ± 467.8	2186.5 ±475
$t_{1/2}$ (days)	4.45 ± 1.53	8.7 ± 1.82	7.8 ± 0.5

Patients undergoing hemodialysis had a shorter $t_{1/2}$ and a reduced AUC. This leads to the speculation that hemodialysis partly contributes to the elimination of the active metabolite. However, it was also seen that the AUC was highest in the patient with the highest extraction ratio (0.26). The sponsor speculates that other factors such as the

differences in protein binding may also contribute to the more rapid elimination in this group of patients.

The dialysis extraction ratio of A77 1726 in hemodialysis subjects was calculated using A77 1726 plasma concentrations in venous blood entering the dialyser (C_{in}) and in blood leaving the dialyser (C_{out}). The mean extraction ratio of A77 1726 for each hemodialysis subject is given in the table below.

The clearance rates from the dialysate were calculated for both creatinine and A77 1726 and are summarized below. The low additional contribution of CAPD to the elimination of A77 1726 is also substantiated by the low mean dialysate clearance of 0.13 ml/min. This can be explained by the high protein binding of the metabolite.

Study Group	Dialysate creatinine clearance (ml/min)[a]	Dialysate A77 1726 clearance (ml/min)[b]
Hemodialysis group (Mean ± SD)	-	32.7 ± 18.7
Subject 1	-	
Subject 2	-	
Subject 3	-	
CAPD group (Mean ± SD)	4.7 ± 0.91	0.13 ± 0.14
Subject 4		
Subject 5		
Subject 6		

[a] $Cl_{creat} = A_{creat}/(t_2-t_0)(C_{creat})$

[b] $Cl_{dial} = Q.ER$, where Q = measured blood flow rate

Concentrations of TFMA in plasma were equal to or below 9.4 ng/ml. Pharmacokinetics of A77 1726 in patients with mild and moderate renal impairment has not been studied.

The effect of dialysis on plasma protein binding of A77 1726 was also determined from study B101 NI patients, the free fraction was in the range between 0.44-1.37% in dialysis patients compared to mean values of 0.52-0.67% measured in healthy subjects at similar concentrations. The results were more variable as compared to normal subjects and rheumatoid patients and showed no obvious pattern relating dialysis to the extent of protein binding. However, there are insufficient number of subjects to make any firm conclusions regarding the influence of dialysis on plasma protein binding of A77 1726.

Conclusions

- This study confirms that in patients with chronic renal failure, free fraction of A77 1726 is likely, but not certain, to be higher than healthy subjects. The free fraction was twice that seen in healthy plasma. Hemodialysis and CAPD had no clear effect on protein binding, but there were too few subjects for any firm conclusions to be drawn.
- The value of dialysis on treatment of over dosage of leflunomide is not significant. A77 1726 is negligibly cleared by dialysis.
- The results from this study are consistent with a poorly soluble drug, with a small volume of distribution and high protein binding.

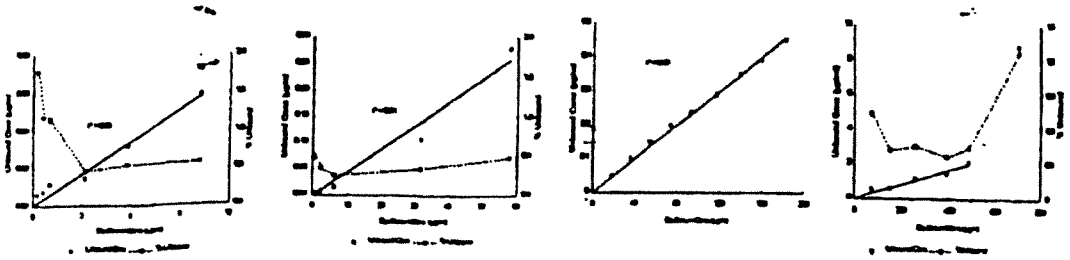
Reviewer's Comment

Leflunomide was not administered under nondialysis or intermittent hemodialysis condition to evaluate the contribution of dialysis on the elimination of A77 1726 in these patients and the patients were not at steady state either.

PROTEIN BINDING

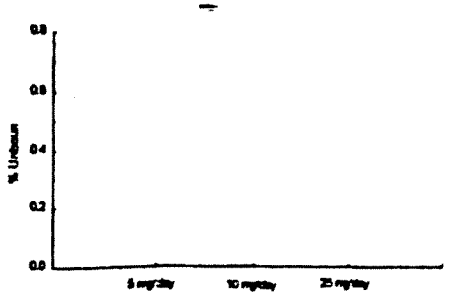
The following observations have been made from the in-vitro protein binding studies.

- There was a reasonably linear relationship between the unbound and total concentrations of leflunomide (Figure below). Although higher at the lower concentrations, the percent unbound was constant from approximately 3 → 10 µg/ml, averaging ~ 0.53 ± 0.06%.
- Binding was independent of concentration at least to ~ 60 µg/ml. The unbound fraction averaged 0.39 ± 0.10% over the concentration range of 10-60 µg/ml.
- The binding of A77 1726 to human serum proteins was examined over a wider concentration range (20 → 200 µg/ml) in vitro by equilibrium dialysis, indicating that binding was independent of concentration. The unbound fraction averaged 0.26 ± 0.01% over this concentration range, consistent with that observed at lower concentrations (0.39 ± 0.10%).
- Protein binding was also studied at higher concentration range of 89 → 839 µg/ml. At concentrations from 89 → 573 µg/ml, the mean binding was 99.5%. But at 839 µg/ml binding was diminished (98.7%) and the free fraction was over double than that seen at lower concentrations.



Plasma A77 1726 concentrations in the pharmacokinetic and clinical studies have typically not exceeded 150 µg/ml. Consequently, the protein binding and the relationship between bound and free should be constant over the range of A77 1726 plasma concentrations observed or expected in the clinical use of leflunomide.

- No relationship between albumin concentration and protein binding could be obtained in another study.



- The protein binding of A77 1726 in RA patients was further investigated using plasma from patients in the multiple dosing study YU204. Plasma was obtained from 4 patients in each of the 3 dosing groups — 5 mg/day (50 mg loading dose), 10 mg/day (100 mg loading dose) and 25 mg/day (100 mg loading dose) — and included unlabelled A77 1726 concentrations ranging from ~4 µg/ml to ~100 µg/ml. As shown in the figure, the percent unbound was comparable in all 3 groups and averaged 0.55% across the 3 groups.
- Due to high protein binding of A77 1726, the potential for protein binding interactions with warfarin, diclofenac, ibuprofen and tolbutamide was investigated in vitro using equilibrium dialysis. The mean percentage change in unbound fraction of the potential interacting drugs in the presence of A77 1726 as used in the in vitro studies are summarized in the Table. The concentration of A77 1726 used was 10, 20 and 50 µg/ml. A77 1726 did not affect binding of warfarin, increased percent unbound of diclofenac by 23 to 50%, increased for ibuprofen, for tolbutamide % unbound increased from 31 to 44%. The protein binding of A77 1726 was not altered in the presence of warfarin, diclofenac or ibuprofen. However, tolbutamide led to an increase in the percent unbound of A77 1726, which was dependent upon the concentration of tolbutamide, but independent of concentration of A77 1726. Mean percent change in unbound fraction[1] of A77 1726 in the presence of tolbutamide is tabulated below.

Drug	Conc (µg/ml)	Mean Percent Change in Unbound Conc
Warfarin	1.0	3.5
	2.5	4.3
	5.0	-14.9
Diclofenac	0.5	50.0
	2.5	22.6
	5.0	47.8
Ibuprofen	20	12.7
	50	25.0
	75	17.0
Tolbutamide	50	43.5
	250	43.9
	400	30.5

	Tolbutamide (µg/ml)		
A77 1726 (µg/ml)	50	250	400
10	50.0	125	200
20	50.0	125	200
50	40.0	80	160
Mean	47.0	110	187

[1]Percent change in binding from value obtained without tolbutamide.

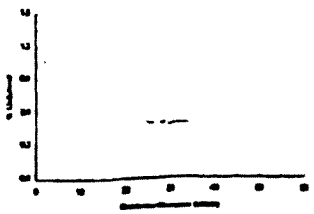
Protein Binding and dialysis

- The in vitro protein binding of A77 1726 was compared in plasma from 6 healthy volunteers, 6 patients with RA, and 12 patients with chronic renal insufficiency, most undergoing CAPD. Binding was determined in vitro with ^{14}C-A77 1726 (100 µg/ml) using equilibrium dialysis and results summarized in the table below.

Population	% Unbound
Healthy Volunteers (n=6)	0.62 ± 0.05
Patients with Rheumatoid Arthritis (n=6)	0.80 ± 0.17
Patients with Chronic Renal Insufficiency (n=12)[a]	1.51 ± 0.41

[a]Combination of groups with fresh and frozen plasma.

- The effect of dialysis on plasma protein binding of A77 1726 was also determined from study B101 NI patients, the free fraction was in the range between 0.44-1.37% in dialysis patients compared to mean values of 0.52-0.67% measured in healthy subjects at similar concentrations. The results were more variable as compared to normal subjects and rheumatoid patients and showed no obvious pattern relating dialysis to the extent of protein binding. However, there are insufficient number of subjects to make any firm conclusions regarding the influence of dialysis on plasma protein binding of A77 1726.
- Protein binding was also performed in a larger group of 50 subjects with chronic renal failure who were not part of study B101 NI. In this group the mean value of free fraction of A77 1726 was slightly higher than that seen in healthy subjects and very similar to that seen in rheumatoid patients. The values of free A77 1726 were in the range of 0.47-1.33%. There was an indication of a relationship between creatinine clearance and free fraction in that generally those patients with the lowest creatinine clearance had the highest free fraction of A77 1726. However, one patient (subject 10) did not fall into this trend (creatinine clearance 7.5 ml/min, free fraction 0.65%). Individual subject data is attached on pages A33 to A34 of the Appendix.



DRUG INTERACTIONS

(A) <u>In Vitro Interactions</u>

The potential inhibitory effects of leflunomide and the three metabolites, A77-1726, N-

(4'-trifluormethylphenyl)-2-cyano-acetamide (A81 3226) and TFMA-oxanilic acid, on cytochrome P450 isoenzymes were investigated using marker substrates and human liver microsomes. The specific marker enzymes and substrates are listed in the Table.

Isoenzyme	Marker Enzyme	Marker Substrate
CYP 1A2	Ethoxyresorufindeethylase	Ethoxyresorufin
CYP 2D6	Bufuralol 1'-hydroxylase	Bufuralol
CYP 3A4	Testosterone 6β-hydroxylase	Testosterone
CYP 2C9	Tolbutamide 4-hydroxylase	Tolbutamide

The strongest inhibitions of all 4 isoenzymes were observed for leflunomide (see Table below). However, at clinical doses of leflunomide, plasma concentrations of the parent compound are rarely observed due to extensive first pass metabolism. Consequently, any interactions with other substrates could only occur during the first pass – with both substrates present – through the liver and/or gut wall. A77 1726 is the major circulating species and appears to inhibit CYP 2C9. Steady-state C_{min} values after dosing with 25 mg/day (Study YU204) averaged 63 µg/ml, corresponding to 243 µM, ~ 13-fold higher than the IC_{50}, implying that A77 1726 has the potential to inhibit the metabolism of CYP 2C9 substrates. Since non-protein bound drug is able to interact with the enzyme, the free plasma concentration may be a better predictor of potential inhibition. Assuming a free fraction of 1.3% in patients with RA, the free plasma concentration would be 3.2 µM, approximately 6-fold lower than the IC_{50}, indicating the likelihood of inhibition.

IC_{50} (µM) for leflunomide and metabolites				
Substance	CYP 1A2	CYP 2D6	CYP 3A4	CYP 2C9
Leflunomide	2.2 ± 1.8	> 1000	51 ± 39	210 ± 120.4
A77 1726	> 500	> 1000	No Inhibition	17.7 ± 71
A81 3226	No Inhibition	> 1000	81.9 ± 133	No Inhibition
TFMA-Oxanilic Acid	No Inhibition	> 1000	No Inhibition	No Inhibition

The potential of A77 1726 to inhibit the metabolism of CYP 2C9 substrates was further investigated in vitro using diclofenac, a non-steroidal anti-inflammatory drug likely to be given concurrently with leflunomide. Non-steroidal anti-inflammatory drugs like diclofenac and piroxicam are substrates for CYP 2C9. Diclofenac (10 µM) was incubated with A77 1726 (0.001 → 1000 µM, corresponding to 0.00026 → 258 µg/ml) in a human liver microsomal preparation and the formation of 4'-hydroxydiclofenac determined. A77 1726 inhibited the formation of 4'-hydroxydiclofenac with an IC_{50} of 64 ± 40 µM. The inhibition appeared to be non-competitive with a Ki of 46 µM. Extrapolating in vitro data of this type to the in vivo situation is difficult. However, the clinical trials showed no differences between patients taking leflunomide concomitantly with diclofenac and those not taking diclofenac, indicating that any potential interaction in man may not be of clinical significance.

(B) <u>In Vivo Interactions</u>

With oral contraceptive, Triphasil® (Study # ZA101):

Study ZA101 examined the effect of leflunomide on antiovulatory effect of a low dose (combination) oral contraceptive agent Triphasil® (levonorgestrel/ethinyl estradiol) in 34 healthy premenopausal Caucasian females.

This study was extended over three menstrual cycles (~12 weeks). After a control cycle to demonstrate ovulation, defined as a serum progesterone concentration > 10 nmol/L, subjects received 2 cycles of Triphasil® (Akromed Products [Pty] Ltd.), the first without leflunomide and the second with leflunomide administered at a dose of 100 mg/day on Days 1 → 3 (loading dose) followed by 20 mg/day on Days 4 → 20. On Days 21 and 22 of the second cycle, 20 g of activated charcoal in 40 ml of water was administered every 6 hours to enhance the elimination of A77 1726. Pre-dose blood samples were collected through 28 days and analyzed for A77 1726 and progesterone. Plasma concentrations were measured during cycle 3 on days 1, 2, 3, 4, 10, 14 and 21 to demonstrate steady-state concentrations and on days 23 and 28 to demonstrate elimination of A77 1726 from the body. Details of study design are given on page A35 of the Appendix.

The mean plasma A77 1726 concentrations (µg/ml)-trough levels are tabulated below.

Day	Mean (µg/ml)	CV%	Range
1	0.08*	-	
2	9.29	20.4	
3	19.6	18.1	
4	29.9	18.8	
10	33.5	19.5	
14	36.3	21.3	
21	39.1	23.0	
23	19.0	53.6	
28	15.5	57.0	
40	8.50	0.00	

* All but 2 subjects had values below LOQ=0.10µg/ml
Protocol violations were made for sampling days for 7 subjects (sampled on day 11, 12, 15, 25, 28, and 32)

By reviewing the individual subject data it was observed that on Day 1 two subjects had detectable levels, 0.90 and 33.9 µg/ml. The applicant has omitted the 33.9 µg/ml value to calculate the mean of 0.08 µg/ml. This observed concentration cannot be explained based on the pharmacokinetics of leflunomide. Protocol violation states that for this subject (#14) the 0 h blood sample was taken 2 minutes after ingestion of leflunomide on day 1. Steady state appears to have reached between days 14 and 21. Rapid elimination was observed with the ingestion of activated charcoal on days 21 to 23, the mean levels decreased from 39 to 19 µg/ml within 2 days (days 21 to 23), thereafter, elimination was notably slower, the mean value decreasing only to 15.5 µg/ml over 5 days (days 23 to 28). The plasma concentration profile is attached on page A36 of the Appendix.

Serum progesterone concentrations were determined to prove ovulation (progesterone concentrations of 10 nmol/l or higher) during cycle 1 and to prove suppression of ovulation during cycles 2 and 3. Subjects enrolled into the study had mean plasma progesterone concentrations indicating that all were ovulating (plasma progesterone > 10 nmol/L). Administration of Triphasil® reduced mean progesterone concentrations to 1.42 nmol/L (see Figure), with a maximum value of 4.57 nmol/L, indicating an antiovulatory effect in all subjects (plasma progesterone ≤ 10

nmol/L). When leflunomide was co-administered with Triphasil®, mean progesterone concentrations were comparable (1.73 nmol/L) (see Figure) and the maximum value was 2.81 nmol/L, indicating no effect of leflunomide on the antiovulatory action of the oral contraceptive. The LOQ for progesterone was 0.3 nmol/l.

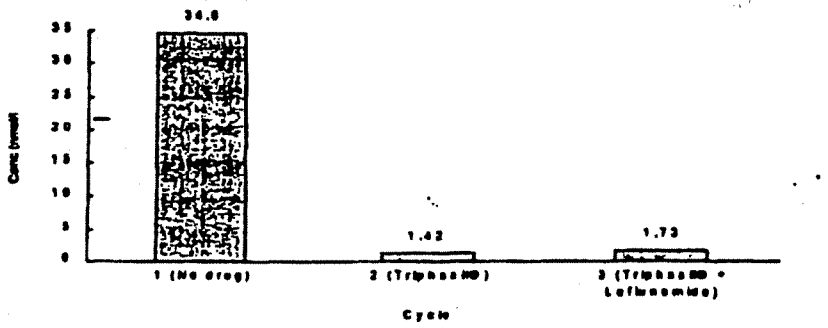


Figure: Effect of Concomitant Administration of Leflunomide and Triphasil® on Mean Plasma Progesterone Concentrations

The risk of ovulation by concomitant treatment of leflunomide and Triphasil® was calculated for solving the following equation for r;

$$\sum_{i=0}^{0} {}^{32}C_i r^i (1-r)^{32-i} = (1-r)^{32} = 0.05$$

and was found to be 8.94%.

Methotrexate (Study # 2 F01):

Methotrexate (MTX) is considered to be the "gold standard" disease modifying antirheumatic drug (DMARD) in the treatment of RA. It is reasonable to expect that patients may receive leflunomide and MTX concomitantly. The primary objective of this study was to evaluate the safety of the addition of leflunomide treatment in subjects whose RA had remained active despite MTX therapy for at least 6 months at doses of ≥ 15 mg/wk, or ≥ 10 mg/wk in the event of documented intolerability. The secondary objectives were to evaluate the pharmacokinetics and potential efficacy of the agents used in combination.....

This study report presents data for the first 12 months of treatment. The planned therapy is for 24 months or as long as the clinical benefit continues. Patients were to have been treated with MTX for at least 6 months, on a stable dose of MTX for ≥ 4 weeks before entry into the study and have active RA. After a leflunomide loading dose of 100 mg/day for 2 days, patients received 10 or 20 mg of leflunomide per day in addition to their weekly dose of MTX, and continued on the combination therapy for 12 months or as long as clinical benefit occurred.

Plasma concentrations for measurement of MTX and/or leflunomide were collected at up to 4 visits from 11 subjects from one center. Visit 1 was prior to leflunomide administration and Visits 2 → 4 occurred 40 to 80 days after the preceding visit, with the

exception of 2 patients for whom Visits 3 and 4 were separated by 449 and 191 days. Other details are on page A37.

As shown in the table below, there was no significant effect of visit (pre and post leflunomide) on any of the methotrexate pharmacokinetic parameters. Maximum A77 1726 plasma concentrations after the first 100 mg loading dose were consistent with that obtained in other studies and no apparent change in C_{max} during the maintenance dose was observed. Maximum concentration of TFMA was also within the limits observed in other studies. Pharmacokinetics of methotrexate and A77 1726 do not seem to be altered in this study. Parent leflunomide concentrations have not been measured.

Table: Mean ± Sd parameters for MTX in patients receiving concomitant leflunomide

Parameter[a]	Baseline Visit 1	Week 6 Visit 2	Week 12 Visit 3	Week 24 Visit 4	p-value[b]
C_{max} (µM/mg)	0.049 ± 0.014	0.052 ± 0.010	0.049 ± 0.013	0.050 ± 0.018	0.7920
t_{max} (hr)	2.06 ± 0.56	1.83 ± 0.83	1.63 ± 0.83	1.56 ± 0.73	0.3523
$AUC_{0\rightarrow 8}$ (hr x µM/mg)	0.18 ± 0.049	0.20 ± 0.033	0.20 ± 0.056	0.19 ± 0.056	0.1735
AUC_{last} (hr x µM/mg)	0.24 ± 0.067	0.28 ± 0.061	0.25 ± 0.087	0.25 ± 0.10	0.3718

[a] C_{max} and the AUCs were normalized for dose. $AUC_{0\rightarrow 8}$: area under the curve to 8 hours; AUC_{last}: area under the curve to the last time point with a concentration > LOQ.
[b] p-value for visit effect from an Analysis of Variance (C_{max} and AUCs) or Wilcoxon Rank Sum Test (t_{MAX})

This can also be demonstrated by the plots of individual values for dose-normalized AUC_{last} and C_{max} as a function of visit.

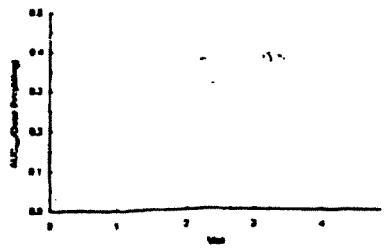


Fig: Dose-normalized MTX AUC_{last}

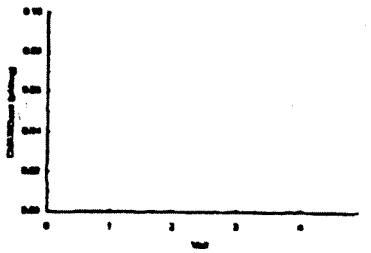


Fig: Dose-normalized MTX C_{max}

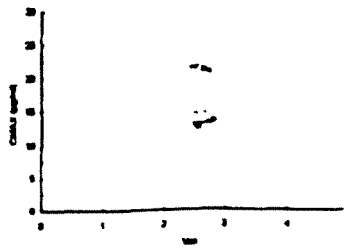


Fig: A77 1726 C_{max}

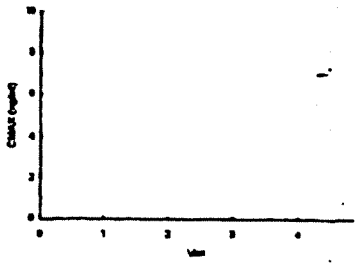


Fig: TFMA C_{max}

Two incidences (subject 55013 and 56005) of grade III-IV elevated LFTs were observed, but unfortunately PK assessment was not done in these subjects, hence the reviewer in unable to make any judgment regarding the correlation between the observed effect and the pharmacokinetic parameter observed from those individuals in this study. These subjects discontinued from the study participation.

Cimetidine (Study #1032):

Leflunomide is metabolized to A77 1726, most likely during presystemic and/or first-pass metabolism, therefore, the potential for drug interaction exists when co-administered with drugs that affect the cytochrome P450 mixed function oxidase system. Cimetidine may alter absorption, compete for renal tubular secretion and affect hepatic blood flow. The objective of this study was to determine the single dose pharmacokinetics of leflunomide and its metabolites A77 1726 and TFMA alone and after multiple doses of cimetidine. Details of the study design are sketched on page A38 of the Appendix. Plasma samples were collected for 120 hours after each leflunomide dose from 12 male subjects and analyzed for leflunomide, A77 1726 and TFMA. Cholestyramine was also administered on day 11.

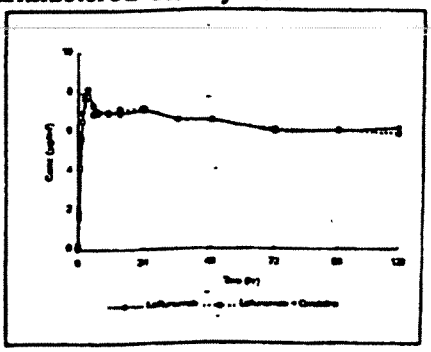


Fig: Mean plasma concentrations of A77 1726 after administration of leflunomide with and without cimetidine (300 mg qidx10days) to healthy volunteers

Mean plasma A77 1726 concentrations were essentially superimposable after administration of leflunomide alone or following 5 days of dosing with cimetidine (see figure). There were no differences between treatments in C_{max} or AUC and the 90% confidence intervals for both parameters were within the 80% → 125% range indicating equivalent exposure to A77 1726 under both conditions.

Mean ± SD pharmacokinetic parameters for A77 1726 and 90% confidence intervals are tabulated below.

Parameter	Leflunomide alone	Leflunomide + Cimetidine	p-value[a]	90% Confidence Interval
C_{max} (µg/ml)	8.33 ± 0.97	8.57 ± 1.58	0.661	94% → 110%
t_{max} (hr)	3.59 ± 1.08	15.0 ± 27.9	N/A	N/A
$AUC_{0 \rightarrow 120}$ (hr x µg/ml)	762.6 ± 88.1	768.0 ± 109	0.986	96% → 104%

[a] p-value from treatment effect of the ANOVA

Leflunomide was detected in the plasma (LOQ 5 ng/ml) sporadically in about 50% of the subjects when leflunomide was administered alone and in 11 of the 12 subjects when

coadministered with cimetidine. The majority of concentrations were ≤ 50 ng/ml, although a few higher concentrations were observed. TFMA could be detected in all subjects at early times after administration of leflunomide. No pharmacokinetic or statistical analyses were performed because of the sparse data. The frequency distribution plots for leflunomide and TFMA is shown below.

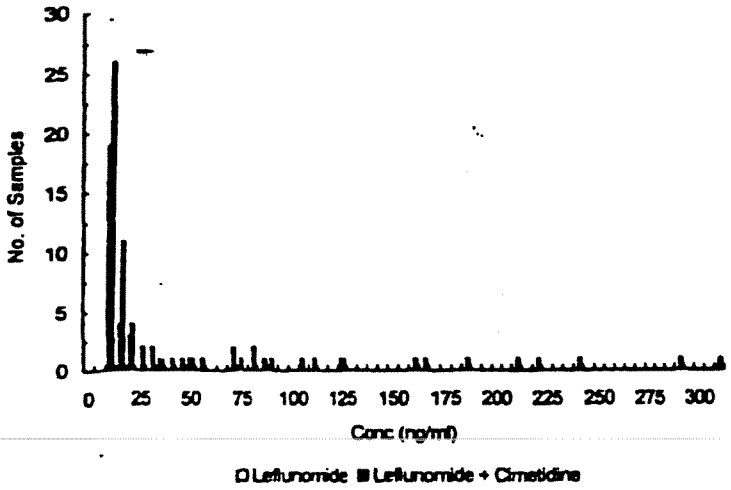


Fig: Frequency distribution of leflunomide plasma concentration

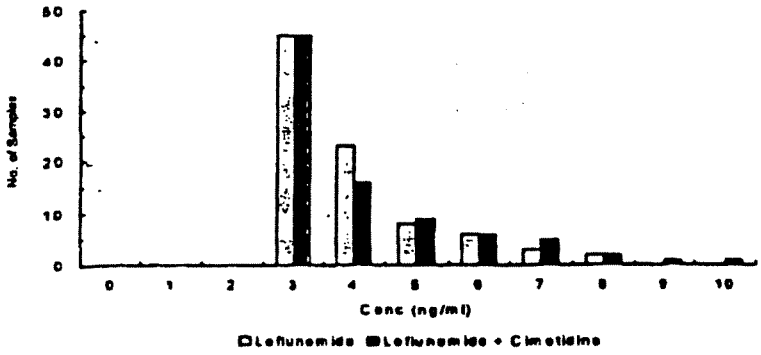
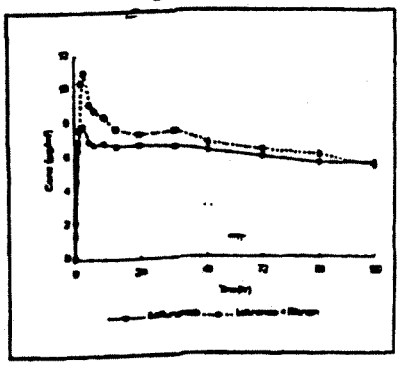


Fig: Frequency distribution of TFMA plasma concentration

The sponsor has taken measures to acidify the plasma pH to 3 to 4 for leflunomide assay upon collection of samples to prevent its breakdown to A77 1726 under basic conditions.

Rifampin (Study # 1033):

Rifampin is a non-specific cytochrome P-450 inducer. The objective of this study was to determine the single dose pharmacokinetics of leflunomide and its metabolites A77 1726 and TFMA alone and after multiple doses of rifampin. Details of study design are sketched on page A39 of the Appendix. Plasma samples were collected for 120 hours after each leflunomide dose from 12 male subjects and analyzed for leflunomide, A77 1726 and TFMA. Cholestyramine was also administered on day 13.



Mean plasma A77 1726 concentrations were higher after administration of leflunomide following 8 days of dosing with rifampin (see figure) and there was a small, but statistically significant increase in C_{max}. The individual subject increase in C_{max} is shown on page A40. Although the increase in AUC was statistically significant, the 90% confidence interval (105% → 115%) was within the 80% → 125% range, indicating that the net exposure to A77 1726 under both conditions was equivalent.

Fig:Mean plasma concentrations of A77 1726 after administration of leflunomide with and without rifampin (300 mg/day x 12days).

Mean ± SD pharmacokinetic parameters for A77 1726 and 90% confidence intervals are tabulated below.

Parameter	Leflunomide alone	Leflunomide + Rifampin	p-value[a]	90% Confidence Interval
C_{max} (µg/ml)	8.17 ± 1.32	11.4 ± 2.02	0.001	129% → 148%
t_{max} (hr)	5.21 ± 5.98	3.17 ± 1.40	N/A	N/A
$AUC_{0 \rightarrow 120}$ (hr x µg/ml)	732.3 ± 74.0	809.5 ± 105	0.003	105% → 115%

[a] p-value from treatment effect of the ANOVA

Seven out of the 12 subjects had detectable plasma concentrations of leflunomide when leflunomide was administered alone and 2 out of the 12 subjects after administration with rifampin. As illustrated in the figure below, the majority of concentrations from the leflunomide-only treatment and all from the combination were ≤ 25 ng/ml. TFMA was observed sporadically in all subjects when leflunomide was administered alone and in most subjects when leflunomide was co-administered with rifampin, with the majority of concentrations for both treatments ≤ 10 ng/ml. Based on these data, rifampin did not appear to induce the formation of TFMA.
The frequency distribution plots for leflunomide and TFMA is shown below.

Fig: Frequency distribution of leflunomide plasma concentration

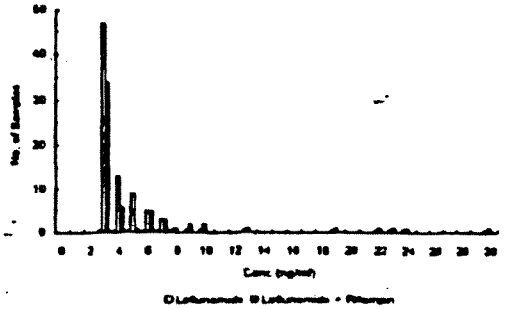


Fig: Frequency distribution of TFMA plasma concentration

Reviewers Comment

Mean plasma concentrations after a single dose of leflunomide are affected in the presence of rifampin, showing a statistically significant increase in C_{max}. The impact on the levels after chronic dosing with leflunomide in the presence of rifampin cannot be assessed from this study, hence, caution must be taken on concomitant administration of leflunomide with rifampin.

BIOEQUIVALENCE

Bioequivalence studies can be difficult for drugs with long elimination half-lives due to the extended period of time required for washouts between treatments. For leflunomide, 5 half-lives, or ~ 40 days in healthy volunteers, would be required between 2 treatments to ensure complete elimination of the previous dose. The applicant has utilized a "pseudo-simultaneous" or "*semi-simultaneous*" method as an alternative design that can result in comparable estimates of bioequivalence while shortening the overall length of the study.

In this approach, the administration of each study formulation is superimposed on the still-continuing elimination of A77 1726 from the preceding dose of leflunomide. Before administration of each study formulation, sufficient samples are taken over an appropriate time period to estimate the concentration time profile originating from the previous dose of leflunomide. The dosing intervals are arranged to ensure that the residual concentrations of A77 1726 in plasma from loading dose or from the first formulation are similar, when the first or second formulations, respectively are administered. Using an estimate of the elimination rate constant (λ_z) and the plasma concentration just prior to dosing, the observed plasma concentration-time curve is then "corrected" for the underlying concentration-time curve before calculation of the pharmacokinetic parameters used to estimate bioequivalence (C_{max}, t_{max}, and AUC).

The utility of the psuedo-simultaneous method for determining the bioequivalence between different formulations of leflunomide was tested in a 6 subject pilot study using 2 administrations of the same batch of 10 mg tablets. Results of this pilot study showed no significant differences between treatments in C_{max}, t_{max}, and AUCs and the 90% equivalence intervals for C_{max} and AUCs were well within the 80%→125% equivalence range in the pilot study. Hence, the applicant feels that this method would be suitable for the assessment of bioequivalence of different formulations of leflunomide. The study design was discussed with the agency during the development phase and was agreed to be an acceptable method. The details of the study design will be described in the following study with the equations used to calculate the corrected concentrations and the AUCs.

<u>10 mg tablets used in clinical trials vs the to-be-marketed tablets</u> (Study # 1036):

Twenty healthy male volunteers received a 20 mg loading dose (2 × 10 mg reference tablets) followed by 10 mg clinical or to-be-marketed tablets at 288 hours (13 days) and

624 hours (27 days), according to a randomized crossover. Plasma samples were collected for a total of 47 days and analyzed for A77 1726. To enhance A77 1726 elimination, 4 gm of cholestyramine was administered TID for 3 days beginning on Day 40. Details of study design and sampling schedule are attached on page A41 of the Appendix. For each treatment, plasma samples obtained 192, 144, 120, 72, and 24 hours before dosing were used to estimate the value of λ_z used to "correct" the observed plasma concentrations for the underlying concentrations from the previous dose. The different time points of the curve used to determine the $t_{1/2}$ and AUCs are also outlined in detail in the Appendix on pages A43-A44.

The main assumption behind using the psuedo-simultaneous approach for bioequivalence studies was that the concentration decline was monoexponential. With this assumption the entire mathematical approach to correcting the carryover effects from the previous dose is logical.

Details of their approach are discussed below. Separate exponential functions were adjusted to the five concentration-time data pairs obtained immediately before administration of each study formulation as follows:

$$C(t)_1 = C(0h)_1.\exp(-\lambda_1.t)$$

where, $C(t)_1$ = adjusted exponential function for the data preceding administration of the first study formulation

$C(0h)_1$ = intercept at study time 0

λ = rate constant

$$C(t)_2 = C(0h)_2.\exp(-\lambda_2.t)$$

where $C(t)_2$, $C(0h)_2$ and λ_2 are the corresponding term from the second study.

The corrected concentration were calculated as follows:

$C(t_i)_{corrected} = C(t_i) - C(0h)_1.\exp(-\lambda_1.t)$ with $288h \leq t_i \leq 408h$

$C(t_i)_{corrected} = C(t_i) - C(0h)_2.\exp(-\lambda_2.t)$ with $624h \leq t_i \leq 744h$

where $C(t_i)$ = observed concentration at time t_i

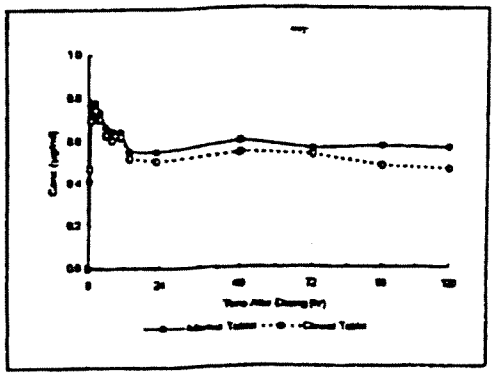
The "corrected" plasma concentration-time data were analyzed using non-compartmental methods. Data through 120 hours after each dose were used in the pharmacokinetic analyses. Although 20 subjects completed the study, only 16 could be evaluated for pharmacokinetics. Of the subjects that were not evaluated, 2 were due to lost samples and 2 were due to aberrant data that prevented calculation of elimination constant and needed to be corrected for previous doses.

AUD (area under concentration-time data) was calculated using linear trapezoidal rule for the first 23, 48, 72, 96 and 120 hours after administration of each study formulation. The area attributable to the carry over of A77 1726 was then subtracted from these AUD values according to the following formulae for the first and second study formulations, respectively.

$AUD(288\text{-}311h)_{corrected} = AUD(288\text{-}311h) - AUC(288\text{-}311h)_1$
$= AUD(288\text{-}311h) - C(288h)_1.(1-\exp((-\lambda_1.23))/\lambda_1$

$AUD(624\text{-}647h)_{corrected} = AUD(624\text{-}647h) - AUC(624\text{-}647h)_2$
$= AUD(624\text{-}647h) - C(624h)_2.(1-\exp((-\lambda_2.23))/\lambda_2$

where, $C(288h)_1$ and $C(624h)_2$ are the corrected concentrations



The mean plasma concentrations after administration of the clinical and market tablets, corrected for carryover from the previous dose or doses, were very similar (see figure). There were no significant differences between treatments in C_{max} or AUC over any of the measured time periods. As shown in the Table, 90% confidence intervals for C_{max} and all AUCs were well within the 80% → 125% equivalence range.

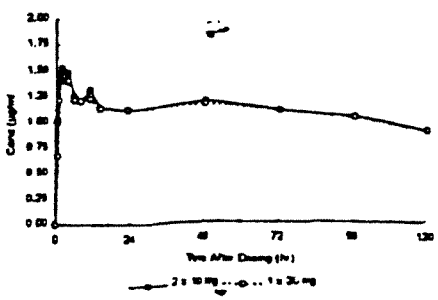
The results of this study demonstrate that the 10 mg leflunomide tablet used in the clinical trials is bioequivalent to that which will be used for marketing.

Parameter	Clinical 10 mg	Market 10 mg	Ratio [%]	90% Confidence Interval
C_{max} (µg/ml)	0.83 ± 0.18	0.88 ± 0.20	107	102% → 113%
T_{max} (hr)	2.00 ± 0.95	10.4 ± 29.4	122	
AUC (hr x µg/ml)				
0 → 23 hr	13.3 ± 3.07	14.0 ± 2.70	106	101% → 111%
0 → 48 hr	26.4 ± 6.68	28.4 ± 5.39	108	101% → 117%
0 → 72 hr	39.3 ± 9.96	42.3 ± 8.38	108	101% → 116%
0 → 96 hr	51.5 ± 13.1	55.9 ± 11.6	109	102% → 116%
0 → 120 hr	62.8 ± 16.8	69.6 ± 14.9	111	103% → 120%

Leflunomide was detected in two plasma samples of one subject with concentrations of 5.3 ng/ml and 5.6 ng/ml on study days 1 and 2.

2x10 mg used in clinical trials vs. 20 mg tablet to-be-marketed (Study # 1030):

The study design was the same as the previous study and is outlined on page A42 of the Appendix. The mean plasma concentrations after administration of 20 mg doses of the 10 mg clinical and 20 mg market tablets, corrected for carryover from the previous dose or doses, were essentially superimposable as shown in the figure. There were no significant differences between treatments in C_{max}, t_{max} or AUC over any of the measured time periods. As shown in the Table, 90% confidence intervals for C_{max} and all AUCs were well within the 80% → 125% equivalence



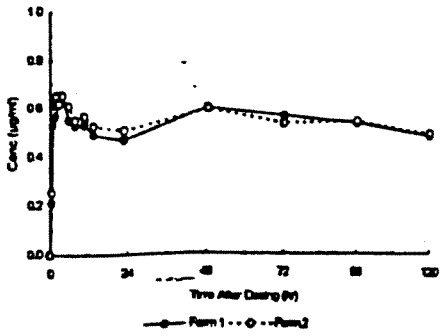
range. The results of this study demonstrate that the 10 mg leflunomide tablet used in the clinical trials is bioequivalent to the 20 mg tablet that will be used for marketing, i.e., the 2 tablets are dosage-form proportional.

Parameter	2 × 10 mg	1 × 20 mg	Ratio [%]	90% Confidence Interval
C_{max} (µg/ml)	1.68 ± 0.42	1.61 ± 0.42	96	90% → 102%
T_{max} (hr)	7.80 ± 14.1	9.20 ± 22.9	100	
AUC (hr x µg/ml)				
0 → 23 hr	26.8 ± 5.57	26.1 ± 6.04	96	92% → 102%
0 → 48 hr	55.6 ± 10.9	54.7 ± 11.8	97	92% → 105%
0 → 72 hr	83.2 ± 16.8	81.8 ± 16.5	97	92% → 105%
0 → 96 hr	109 ± 23.0	107 ± 20.7	98	93% → 105%
0 → 120 hr	132 ± 28.2	130 ± 25.0	98	93% → 105%

Plasma concentrations of leflunomide were below the lower limit of quantitation in most subjects, except in 5, where the values ranged from 5.2-7.2 ng/ml on days 2 and 3.

10 mg tablets using two different crystalline forms of the drug (Study #1035):

Form I and II are the two polymorphic forms of leflunomide which have the same solubility and dissolution profiles. The mean plasma concentrations after administration of 10 mg doses of the tablets prepared from Forms I and II, corrected for carryover from the previous dose or doses, were essentially superimposable as shown in the figure. However, it cannot be concluded from the parametric statistical analysis that the formulations were bioequivalent. As shown in the Table, the 90% equivalence interval for C_{max} was within the 80% → 125% equivalence range. However, the lower limit for the AUCs were < 80%. This was due to a higher variability in the data (39% CV) in this study compared to that observed in previous studies using the same design (12%). This was a consequence of longer than usual values for t½ in some subjects following the loading dose, leading to overestimation of the carryover of concentrations from that dose and affecting the AUC calculations for the first study period. The distribution of log-transformed AUD values after correction for carryover was skewed on Day 1, but not on study Day 2. This skewing was not apparent in the data from the previous two bioequivalence studies employing the same study design. The resultant skewing of AUC values adversely affected the estimates of the confidence intervals.



The sponsor has requested that a nonparametric analysis of the data be acceptable to judge the bioequivalence between two forms of leflunomide. When calculated using a post-hoc nonparametric analysis, confidence intervals for C_{max} and all AUCs were within the 80% → 125% range (see Table below).

			90% Confidence Interval	
Parameter	Form 1	Form 2	Parametric	Non-Parametric
C_{max} (µg/ml)	0.79 ± 0.16	0.81 ± 0.17	91% → 116%	91 → 112
T_{max} (hr)	11.8 ± 18.3	22.0 ± 29.0		
AUC (hr x µg/ml)				
0 → 23 hr	12.5 ± 3.39	11.7 ± 3.27	74% → 113%	88 → 112
0 → 48 hr	26.2 ± 7.42	25.0 ± 7.09	74% → 118%	87 → 112
0 → 72 hr	39.6 ± 11.5	38.8 ± 11.8	75% → 121%	87 → 119
0 → 96 hr	52.4 ± 15.2	51.9 ± 16.3	76% → 122%	88 → 119
0 → 120 hr	64.7 ± 19.3	61.1 ± 20.1	77% → 121%	87 → 117

The results of this study demonstrate that although the polymorphic forms of leflunomide were not bioequivalent when inference is based on the parametric statistical analyses, they produce comparable plasma A77 1726 concentration-time curves.

Reviewer's Comment

The non-parametric test is not acceptable from the bioequivalence standpoint. The applicant had stated that Form II is present to the extent of <10% in a batch, however, it is also mentioned that the proportion of Form II tended to increase during storage. The polymorphic composition of the batches used in clinical and pharmacokinetic studies was requested by the reviewer along with stability information of Form II in a batch of the drug product. The data showed an increase of 7% of Form II in 12 months at 25°C/60% RH. The percentages of Form II at 3 months in the batches 31, 32 and 33 were 2%, 27% and 11%. The percent of Form II in a given batch appears to be quite random. The percentages increasd to 3%, 34% and 15%, respectively for the three batches at the end of 12 months. The pure Form II is not bioequivalent to Form I, but we cannot say that what percentage of Form II in a batch would really affect the bioavailability of the drug product. Hence, it would be recommended that the sponsor is able to prove the given percent in a batch would not make any difference. Recommendations have been given at the end of the review.

POPULATION PHARMACOKINETICS

The population pharmacokinetics section was reviewed with Dr. He Sun (Pharmacometric node for DPE III)

Two kinds of population analysis was done by the sponsor:

- *Interaction with charcoal/cholestyramine*: Total CL was 10 times higher than normal values. On average the effect from a single charcoal/cholestyramine lasted 7.1 h. Approximately 18.5% and 10.5% of the available A77 1726 was extracted from the body in men and women, respectively following a single dose.
- *Kidney disease*: Patients with kidney disease showed significantly increased CL (24%) and V (43%), resulting in increased half life (16%).

RA Patients

- *Age*: Age was used as a categorical value (below and above 53 yrs). CL of older group was 18.7% lower than that of younger group and t1/2 was 18.5% higher.
- *Body Size*: Height best related to CL and V.
- *Sex*: CL in women was 22% lower than in men.

Although age, sex, and height were statistically significant as single covariates in RA patients, there was no major reduction in variability by the combined model. The median values for CL and V in healthy subjects and patients with RA are listed in the following Table. These values are in good agreement with those obtained in Study 1024, in which healthy volunteers received 10 mg of A77 1726 by intravenous infusion. The mean values for CL and V were 31.3 ml/h and 10.6 L, respectively.

Median (95% CI) Pharmacokinetic Parameter Estimates in Healthy Subjects and Patients with RA		
Parameter	**Healthy Subjects**	**Patients with RA**
CL (ml/h)	30.1	26.9
V (L)	9.9	16.1

(B) Phase III Analysis

The Phase III analysis was using data from 742 of the 816 (91%) patients in the Phase III studies that received leflunomide. The demographics of the patients from the Phase III studies are summarized in the Table.

Summary of Demographic Data for Patients from the Phase III Studies	
Parameter	**Mean ± SD**
Age (yr)	58 ± 11
Weight (kg)	72 ± 14
Height (cm)	164 ± 9.0
Lean Body Mass (kg)	50 ± 9.0
Liver Function Tests	
SGOT (U/L)	20 ± 6.7
SGPT (U/L)	20 ± 10
SGGT (U/L)	39 ± 46

The following covariates were examined for potential effect on CL and/or V.

Continuous: age, weight, height, lean body mass, liver function tests (SGOT, SGPT, SGGT), renal function

Discrete: age (> 65 vs ≤ 65), sex (male vs female), smoking status (active, former, non-smoker), alcohol consumption (none, < 1 drink/day, ≥ 1 drink per day), SGOT (normal – ≤ 50 U/L, high – > 50 U/L)

Model development was done using the data from 491 patients in Study 302, validated using the data from 251 patients in Studies 301 and 303, and then finalized using data from all 742 patients. Smoking status, SGOT (as a continuous variable), and lean body mass were the significant covariates. The final equations for CL and V were as follows.

$$CL = 23.0 \times (1 + SMOK \times 0.383) \times \left(\frac{20}{SGOT}\right)^{0.097}$$

and

$$V = 11.5 \times \left(\frac{LBM}{50}\right)^{0.372}$$

Conclusions

As noted above for the Phase I/II analysis, the estimates of CL and V were consistent with those estimated from i.v. administration of A77 1726.

- *Smoking*: Smoking appeared to have the greatest impact on CL, with a 38% increase in patients that were active smokers.
- *Liver Function*: The clearance was decreased in patients with increased liver enzymes (SGOT and SGPT). When SGOT increases to 100 u/L, a 15% decrease in CL was calculated.
- *Sex*: There were also modest increases in CL (20%) and V (18%) in male as compared to female patients.
- *Age*: Although age was a signficiant covariate in the Phase I/II analysis, age as either a continuous or discrete variable was not a significant covariate in the Phase III analysis, which is more representative of the target population.
- *Drug-Interactions*: The drugs that were most commonly administered with leflunomide were acetaminophen (40%), diclofenac (32%), prednisolone (18%), folic acid (16%), prednisone (16%), and naproxen (13%). Cimetidine and ranitidine also showed no significant interactions. None of these drugs had a demonstrable effect on the clearance of A77 1726.
- *Interaction with cholestyramine*: Of the 742 patients, only 7 received cholestyramine, and demonstrated a 40% increase in CL, consistent with observations from phase I/II analysis.
- No leflunomide was detected in any of the samples (163 samples). TFMA concentration was not detectable in 66 samples (25%) and was measurable in 202

samples (75%), although concentrations were < 25 ng/ml did not appear to increase over time.

- Based on the Phase I/II population analysis, a plasma A77 1726 concentration of 13 µg/ml appeared to give the maximum probability of a positive response. In the Phase III analysis, 96% of patients had a steady-state concentration > 13 µg/ml after daily administration of 20 mg of leflunomide, including patients with increased clearance as a consequence of smoking. Cholestyramine was the only concomitant medication to affect the pharmacokinetics of A77 1726, an interaction that is known and recommended for enhancing elimination. It appears, therefore, that 20 mg per day is sufficient for most RA patients regardless of demographics or concomitant medication.

Reviewer's Comments

- *The sponsor had three types of data set, (1) data set with blood samples with known dosing and sampling time (N=1964), (2) data set with blood samples with at least one known (N=2642) and (3) data set include large amount of samples without dosing and sampling time information (N=8013).*

  Upon the reviewers request, the sponsor conducted population PK analysis for each of the three data sets. Comparison of the results showed that the structural parameters were not significantly different among the three analysis while variance parameters are somewhat different. Considering the fact that the half-life of the drug is 10-20 days and the maximum error in time recording may not exceed 1 day, increasing sample size will increase the accuracy of variance parameter, and the validation results, the analysis results based on the 2nd data set (n=2624) was accepted.

- *The treatment of outliers was questioned. Upon the review of sponsors response, since the majority outliers are those blood samples with zero observations. The treatment of outliers was acceptable.*
- *The Validation procedure is well conducted and accepted. The reviewer appreciated the sponsor's effort in the validation of the final model.*
- *The findings of the study results contributed to the overall understanding of the pharmacokinetics of A77 1726. The contributions of covariance to the CL and Vd of the drug should be included in the drug labeling for prescription information.*
- *Gender effect appears to be statistically significant. Such differences will be enhanced between male smokers and female non-smokers, and, maybe at a clinically significant level.*

IN VITRO DISSOLUTION

For leflunomide two polymorphic forms (I and II) are known which are practically insoluble in aqueous media. The solubility at 25°C was found to be at 23 mg/l at pH 1.2,

and 21 mg/l at pH 4.8 and pH 6.8 demonstrating independence of the pH of the solvent.

Test Conditions

Acceptance Criteria:

Conclusions

- *Influence of dissolution medium*: For 10 and 20 mg tablets dissolution profiles were identical for water and HCl. Dissolution complies with specification irrespective of medium.
  For 100 mg tablets rapid and complete dissolution occurs

- *Influence of agitation*: 10 mg tablets were not influenced by agitation. The 20 mg and 100 mg tablet were slightly influenced by agitation.

- *Influence of different specific surface area*: Low dissolution rates were found for tablets containing leflunomide For tablets containing drug substance having SSA within the specified range dissolution was within the specified range.

- *Influence of polymorphism*: Dissolution is not influenced by polymorphism. significantly, however a lower trend towards dissolution of tablets was seen that contained the combination of I and II (75:25) and pure Form II.

- Based on the pharmacokinetic characteristic of leflunomide, dissolution of tablets has no or minimal influence of pharmacokinetics and cannot be a rate limiting step regarding bioavailability and can only be used to characterize batch to batch uniformity. T_{max}, the clinical marker for absorption rate is dependent on both absorption rate and elimination rate. Because of the elimination process being longer for leflunomide compared to absorption, the sensitivity of T_{max} to changes in absorption will be smaller than with other drugs with faster elimination. The choice of loading dose depends on the maintenance dose, dosing interval, rate of absorption

and rate of elimination. In a pilot study, a plot of ideal loading dose/maintenance dose ratio as a function of absorption rate was constant.

Reviewer's Comment

- *The choice of this surfactant has not been discussed by the applicant. This medium will not simulate the physiological conditions, hence the dissolution test can only be used for batch to batch uniformity and in vivo performance of the 100 mg tablet cannot be assessed from the dissolution test. However, the 100 mg tablet is to be used for a loading dose only.*
- *The specifications for the dissolution could be tightened a bit. Looking at the dissolution plots it was observed that was dissolved in 30 minutes. Upon agreement with the Chemist, the specifications for the dissolution of leflunomide tablets should be changed to not less than in 30 minutes. The applicant had made a statement in the chemistry section of the NDA that the specifications of in 30 minutes was agreed by the FDA division of Biopharmaceutics. However, the agency had allowed the above specification, but not agreed to it.*

V. Overall Conclusions

- Leflunomide is extensively converted to the active metabolite A77 1726 during the absorption process by presystemic and/or hepatic first pass metabolism.
- The bioavailability of a 100 mg oral tablet relative to a solution was 80%.
- Leflunomide does not show any food effect at the 20 mg dose. Clinical trials (US 301 and MN 302) have been done irrespective of diet restrictions, however, the clinical trial MN 301 specifies doses to be taken with food.
- In patients with RA, the pharmacokinetics of A77 1726 are linear at doses from 5 mg to 25 mg per day. However, the variability was high in the 25 mg group. Steady state concentrations reached within 7 to 8 weeks, the elimination half-life is ~ 15 days. The 10 and 20 mg tablet are dose and dosage form proportional.
- In Phase II studies, plasma A77 1726 concentrations appear to be higher in female RA patients than in males, and among female patients, appear to increase with increasing age. However, age and gender were not significant covariates in the population pharmacokinetic analyses of the Phase III studies.
- If required for the treatment of overdose or toxicity, the elimination of A77 1726 can be enhanced by oral administration of activated charcoal or cholestyramine.
- The percent unbound to plasma protein for leflunomide averaged 0.53 ± 0.06% at concentrations ranging from 3 → 10 µg/ml and 0.4% for A77 1726 over the range 0.75 → 573 µg/ml. In patients with RA, the unbound fraction of A77 1726 was ~ 0.8%.
- A77 1726 caused slight changes (≤ 50%) in the percent unbound of warfarin, diclofenac, ibuprofen, and tolbutamide. Warfarin, diclofenac, or ibuprofen did not alter the protein binding of A77 1726. However, tolbutamide led to an increase in the

percent unbound of A77 1726 that was dependent upon the concentration of tolbutamide but not on the concentration of A77 1726.

- In vitro data suggests that A77 1726 may inhibit cytochrome P450 isoenzyme 2C9 and thus could inhibit the metabolism of CYP 2C9 substrates, such as diclofenac. However, analysis of the safety data in the Phase III studies showed no differences between patients taking leflunomide concomitantly with diclofenac and those not taking diclofenac, indicating that any potential interaction in man is not of clinical significance.
- Leflunomide did not affect the antiovulatory effect of an oral contraceptive (Triphasil®).
- The pharmacokinetics of A77 1726 and MTX do not appear to be altered by concomitant administration of leflunomide and MTX.
- There were no differences in the pharmacokinetics of A77 1726 when leflunomide was administered with cimetidine, a nonspecific cytochrome P450 inhibitor.
- Although plasma concentrations of A77 1726 were higher when leflunomide was co-administered with rifampin, a nonspecific cytochrome P450 inducer, AUCs were equivalent, indicating that the net exposure to A77 1726 was the same under both conditions. However, it is important to give consideration to the AUCs under steady-state conditions, unlike the single dose AUCs observed in the trial.
- The 10 mg tablet used in the clinical trials is bioequivalent to the 10 mg tablet intended for marketing, and when given at the same dose, bioequivalent to the 20 mg tablet intended for marketing.

Unresolved Issue

1. The applicant has requested the agency to allow the usage of 5 x 20 mg tablets as an alternative to 1 x 100 mg tablet as the loading regimen and would like to know whether the agency concurs that an in vivo bioavailability study between 1 x 100 mg and 5 x 20 mg tablet would not be warranted. This will be addressed separately and is not an approvability issue for the application N 20-905.

VI. Comments to be sent to the sponsor

1. The bioequivalence studies showed that pure polymorphic forms I and II were bio-inequivalent from the biopharmaceutics stand point by the acceptable parametric method. The non-parametric method is not acceptable by the agency. The stability of form II in leflunomide 100 mg tablets at 25°C/60% RH showed a maximum increase of 7% in form II in 12 months. The percentages of form II at 3 months in drug product batches 31, 32 and 33 were 2%, 27% and 11%, respectively. The applicant needs to either give specifications for the percent of form II in a particular drug product, or demonstrate bioequivalence in a ratio of 70:30 of form I:II or the maximum intended ratio of I:II in a given drug product, or demonstrate by clinical studies that the percentage of polymorphic form II in a particular batch does not compromise the efficacy or safety of the product.

2. The recommended dissolution specifications should be changed from Q of in 30 minutes to Q of in 30 minutes based on the dissolution data submitted.

7/15/98

Veneeta Tandon, Ph.D.
Pharmacokineticist
Division of Pharmaceutical Evaluation III

Team Leader: E. Dennis Bashaw, Pharm. D. 7/25/98

CC: NDA 20-905 (orig)
HFD-550/Div File
HFD-550/CSO/Cook
HFD-880(Bashaw/Tandon)
HFD-880(Lazor)
HFD-344(Viswanathan)
attn:CDR.B.Murphy

AE

APPEARS THIS WAY
ON ORIGINAL

Clinical Pharmacology/Biopharmaceutics Review

NDA: 20-905 (053) SUBMISSION DATE: 8/21/98

PRODUCT: Leflunomide Tablets

SPONSOR: Hoechst Marion Roussel, Inc REVIEWER: Veneeta Tandon, Ph.D.

Response to Comments

- Response to Item 3 dated August 20th, 1998

Upon consideration of the data submitted we concur with the setting of a specification of no more than , of leflunomide Form II in the drug product.

- Response to Item 4 dated August 20th, 1998

Examination of the data provided for the 20 mg tablet suggests that there would be up to a ~ 18% failure rate for individual tablets, using a specification. On the basis of this we recommend that a dissolution specification of at 30 minutes be adopted. In practice at the S1 level this would result in a specification of : in 30 minutes according to the current USP 23 acceptance table for immediate release drug products.

8/26/98

Veneeta Tandon, Ph.D.
Pharmacokineticist
Division of Pharmaceutical Evaluation III

Team Leader: E. Dennis Bashaw, Pharm. D. 8/26/98

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CM